

**Zinc, Zinc Salts and Zeolites  
Amended Final Work Plan  
Registration Review**

**Case Number: 4099**

Approved By:

  
\_\_\_\_\_  
Jennifer McLain

Acting Director, Antimicrobials Division

Date:

12/14/12  
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## **Zinc, Zinc Salts and Zeolites AMENDED FINAL WORK PLAN**

### **Introduction**

This document amends the *Final Work Plan* (FWP) for the registration review of Zinc, Zinc Salts and Zeolites. Since the publication of the September 2009 Final Work Plan, the Agency has reviewed the data requirements previously identified to support the registration review of Case 4099 (Zinc, Zinc Salts and Zeolites). This document amends the September 2009 FWP to clarify the requirements and remove the following studies which will no longer be required to support the risk assessment:

- 835.1110: Activated Sludge Sorption Isotherm
- 835.1240: Leaching and adsorption/desorption
- 835.2240: Photodegradation in water
- 835.2410: Photodegradation in soil
- 835.4100: Aerobic soil metabolism
- 835.4400: Anaerobic aquatic metabolism
- 870.3100<sup>1</sup>: 90-day Oral Toxicity-rodent
- 870.3150<sup>1</sup>: 90-day Oral Toxicity-non-rodent
- 870.3250<sup>1</sup>: 90-day Dermal- rodent
- 870.3700<sup>1</sup>: Developmental Toxicity-rodent
- 870.3800<sup>1</sup>: Reproductive Toxicity- rodent

Unless otherwise stated by the Agency, all other elements of the Agency's September 2009 Zinc, Zinc Salts and Zeolites FWP remain unchanged.

### **Summary of Data Requirements**

Summary tables of the data required to support the registration review of each of the five active ingredients in the Zinc, Zinc Salts and Zeolites Case (Zinc chloride (PC Code 087801), Zinc oxide (PC Code 088502), Zinc sulfate (PC Code 089001), Zinc (PC Code 129015), and Zinc sulfate monohydrate (PC Code 527200)) are presented below.

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<sup>1</sup> These studies are no longer needed for risk assessment because information to assess potential risk to zeolite compounds will be submitted in response to the silver zeolite DCI anticipated to be issued as part of the Silver Compounds registration review (Case 4082 and Case 5015).

## Data Requirements for the Registration Review of Zinc Oxide (PC Code 088502)

Guideline Number	Anticipated Data Requirement	Test Material	Estimated Timeframe (Measured in months from DCI receipt)
850.3300 or OECD 209 <sup>2,3,4</sup>	Activated Sludge Respiration Inhibition	TGAI	12
835.1230 <sup>2</sup>	Sediment and soil adsorption/desorption	TGAI	12
850.4100 <sup>3,5,6,7</sup>	Seedling emergence, Tier II	TGAI	12
850.4250 <sup>5,6</sup>	Vegetative vigor dose response test using rice ( <i>Oryza sativa</i> )	TGAI	12
850.4400 <sup>2,3,4,6</sup>	Aquatic plant growth using floating macrophyte <i>Lemna gibba</i>	TGAI	12
850.4500 <sup>2,3,6,8</sup>	Aquatic Plant Growth (green alga, freshwater diatom, saltwater diatom)	TGAI	12
850.4550 <sup>2,3,6,9</sup>	Aquatic Plant Growth (cyanobacteria)	TGAI	12
SS <sup>5,10</sup>	Aquatic Leaching from Wood	TGAI	24
SS <sup>5,11</sup>	Soil Leaching from Wood	TGAI	24

<sup>2</sup> Study is required to support the registration review of wood preservative uses, material preservative uses, and outdoor moss control uses.

<sup>3</sup> Analytical measurements of zinc (total, dissolved, and free) and the following water quality parameters that are critical to metal speciation in solution are required: temperature, pH, dissolved organic carbon (distribution of humic and fulvic acids), major cation (Ca, Mg, Na and K), major anions (SO<sub>4</sub> and Cl), alkalinity, and sulfide content.

<sup>4</sup> Because applied zinc and zinc salts will react in aqueous solutions to form free zinc ion and dissolved complexes, the Agency recognizes there is potential for tests conducted with one zinc active ingredient to potentially bridge to another. However, the Agency also recognizes that the content and formation of the free zinc ion and complexes in a test can be affected by dissolution and reaction kinetics and therefore data generated for one of the more soluble zinc active ingredient forms is recommended for use in such bridging.

<sup>5</sup> Study is required to support the registration review of wood preservative uses.

<sup>6</sup> Results from a tier II study are required to be submitted to satisfy this requirement.

<sup>7</sup> Seedling emergence was presented in the Final Work Plan as 850.4225; however, test guidelines 850.4100 and 850.4225 were merged and harmonized into OCSPP 850.4100 in a Federal Register Notice dated June 27, 2012 (FRL-9333-1).

<sup>8</sup> Results for three species (*Selenastrum capricornutum* (green alga), one freshwater diatom, and one saltwater diatom) are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>9</sup> Results for one species of cyanobacteria are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>10</sup> For guidance, please refer to: Standard Method of Determining the Leachability of Wood Preservatives, American Wood Preservers' Association (AWPA) Standard E11-06 or E11-12.

<sup>11</sup> For guidance, please refer to: Standard Method of Determining the Leachability of Wood Preservatives in Soil Contact, American Wood Preservers' Association (AWPA) Standard E20-06 or E20-08.

**Data Requirements for the Registration Review of Zinc Chloride (PC Code 087801)**

<b>Guideline Number</b>	<b>Anticipated Data Requirement</b>	<b>Test Material</b>	<b>Estimated Timeframe (Measured in months from DCI receipt)</b>
850.3300 or OECD 209 <sup>1,2,3</sup>	Activated Sludge Respiration Inhibition	TGAI	12
835.1230 <sup>1</sup>	Sediment and soil adsorption/desorption	TGAI	12
850.4400 <sup>1,2,3,4</sup>	Aquatic plant growth using floating macrophyte <i>Lemna gibba</i>	TGAI	12
850.4500 <sup>1,2,4,5</sup>	Aquatic Plant Growth (green alga, freshwater diatom, saltwater diatom)	TGAI	12
850.4550 <sup>1,2,4,6</sup>	Aquatic Plant Growth (cyanobacteria)	TGAI	12

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<sup>1</sup> Study is required to support the registration review of wood preservative uses, material preservative uses, and outdoor moss control uses.

<sup>2</sup> Analytical measurements of zinc (total, dissolved, and free) and the following water quality parameters that are critical to metal speciation in solution are required: temperature, pH, dissolved organic carbon (distribution of humic and fulvic acids), major cation (Ca, Mg, Na and K), major anions (SO<sub>4</sub> and Cl), alkalinity, and sulfide content.

<sup>3</sup> Because applied zinc and zinc salts will react in aqueous solutions to form free zinc ion and dissolved complexes, the Agency recognizes there is potential for tests conducted with one zinc active ingredient to potentially bridge to another. However, the Agency also recognizes that the content and formation of the free zinc ion and complexes in a test can be affected by dissolution and reaction kinetics and therefore data generated for one of the more soluble zinc active ingredient forms is recommended for use in such bridging.

<sup>4</sup> Results from a tier II study are required to be submitted to satisfy this requirement.

<sup>5</sup> Results for three species (*Selenastrum capricornutum* (green alga), one freshwater diatom, and one saltwater diatom) are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>6</sup> Results for one species of cyanobacteria are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

### Data Requirements for the Registration Review of Zinc Sulfate (PC Code 089001)

Guideline Number	Anticipated Data Requirement	Test Material	Estimated Timeframe (Measured in months from DCI receipt)
850.3300 or OECD 209 <sup>1,2,3</sup>	Activated Sludge Respiration Inhibition	TGAI	12
835.1230 <sup>1</sup>	Sediment and soil adsorption/desorption	TGAI	12
850.4400 <sup>1,2,3,4</sup>	Aquatic plant growth using floating macrophyte <i>Lemna gibba</i>	TGAI	12
850.4500 <sup>1,2,4,5</sup>	Aquatic Plant Growth (green alga, freshwater diatom, saltwater diatom)	TGAI	12
850.4550 <sup>1,2,4,6</sup>	Aquatic Plant Growth (cyanobacteria)	TGAI	12

<sup>1</sup> Study is required to support the registration review of wood preservative uses, material preservative uses, and outdoor moss control uses.

<sup>2</sup> Analytical measurements of zinc (total, dissolved, and free) and the following water quality parameters that are critical to metal speciation in solution are required: temperature, pH, dissolved organic carbon (distribution of humic and fulvic acids), major cation (Ca, Mg, Na and K), major anions (SO<sub>4</sub> and Cl), alkalinity, and sulfide content.

<sup>3</sup> Because applied zinc and zinc salts will react in aqueous solutions to form free zinc ion and dissolved complexes, the Agency recognizes there is potential for tests conducted with one zinc active ingredient to potentially bridge to another. However, the Agency also recognizes that the content and formation of the free zinc ion and complexes in a test can be affected by dissolution and reaction kinetics and therefore data generated for one of the more soluble zinc active ingredient forms is recommended for use in such bridging.

<sup>4</sup> Results from a tier II study are required to be submitted to satisfy this requirement.

<sup>5</sup> Results for three species (*Selenastrum capricornutum* (green alga), one freshwater diatom, and one saltwater diatom) are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>6</sup> Results for one species of cyanobacteria are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

### Data Requirements for the Registration Review of Zinc (PC Code 129015)

Guideline Number	Anticipated Data Requirement	Test Material	Estimated Timeframe (Measured in months from DCI receipt)
850.3300 or OECD 209 <sup>1,2,3</sup>	Activated Sludge Respiration Inhibition	TGAI	12
835.1230 <sup>1</sup>	Sediment and soil adsorption/desorption	TGAI	12
850.4400 <sup>1,2,3,4</sup>	Aquatic plant growth using floating macrophyte <i>Lemna gibba</i>	TGAI	12
850.4500 <sup>1,2,4,5</sup>	Aquatic Plant Growth (green alga, freshwater diatom, saltwater diatom)	TGAI	12
850.4550 <sup>1,2,4,6</sup>	Aquatic Plant Growth (cyanobacteria)	TGAI	12

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<sup>1</sup> Study is required to support the registration review of wood preservative uses, material preservative uses, and outdoor moss control uses.

<sup>2</sup> Analytical measurements of zinc (total, dissolved, and free) and the following water quality parameters that are critical to metal speciation in solution are required: temperature, pH, dissolved organic carbon (distribution of humic and fulvic acids), major cation (Ca, Mg, Na and K), major anions (SO<sub>4</sub> and Cl), alkalinity, and sulfide content.

<sup>3</sup> Because applied zinc and zinc salts will react in aqueous solutions to form free zinc ion and dissolved complexes, the Agency recognizes there is potential for tests conducted with one zinc active ingredient to potentially bridge to another. However, the Agency also recognizes that the content and formation of the free zinc ion and complexes in a test can be affected by dissolution and reaction kinetics and therefore data generated for one of the more soluble zinc active ingredient forms is recommended for use in such bridging.

<sup>4</sup> Results from a tier II study are required to be submitted to satisfy this requirement.

<sup>5</sup> Results for three species (*Selenastrum capricornutum* (green alga), one freshwater diatom, and one saltwater diatom) are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>6</sup> Results for one species of cyanobacteria are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

**Data Requirements for the Registration Review of Zinc Sulfate Monohydrate (PC Code 527200)**

Guideline Number	Anticipated Data Requirement	Test Material	Estimated Timeframe (Measured in months from DCI receipt)
850.3300 or OECD 209 <sup>1,2,3</sup>	Activated Sludge Respiration Inhibition	TGAI	12
835.1230 <sup>1</sup>	Sediment and soil adsorption/desorption	TGAI	12
850.4400 <sup>1,2,3,4</sup>	Aquatic plant growth using floating macrophyte <i>Lemna gibba</i>	TGAI	12
850.4500 <sup>1,2,4,5</sup>	Aquatic Plant Growth (green alga, freshwater diatom, saltwater diatom)	TGAI	12
850.4550 <sup>1,2,4,6</sup>	Aquatic Plant Growth (cyanobacteria)	TGAI	12

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<sup>1</sup> Study is required to support the registration review of wood preservative uses, material preservative uses, and outdoor moss control uses.

<sup>2</sup> Analytical measurements of zinc (total, dissolved, and free) and the following water quality parameters that are critical to metal speciation in solution are required: temperature, pH, dissolved organic carbon (distribution of humic and fulvic acids), major cation (Ca, Mg, Na and K), major anions (SO<sub>4</sub> and Cl), alkalinity, and sulfide content.

<sup>3</sup> Because applied zinc and zinc salts will react in aqueous solutions to form free zinc ion and dissolved complexes, the Agency recognizes there is potential for tests conducted with one zinc active ingredient to potentially bridge to another. However, the Agency also recognizes that the content and formation of the free zinc ion and complexes in a test can be affected by dissolution and reaction kinetics and therefore data generated for one of the more soluble zinc active ingredient forms is recommended for use in such bridging.

<sup>4</sup> Results from a tier II study are required to be submitted to satisfy this requirement.

<sup>5</sup> Results for three species (*Selenastrum capricornutum* (green alga), one freshwater diatom, and one saltwater diatom) are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.

<sup>6</sup> Results for one species of cyanobacteria are required to fulfill requirement. If the NOAEC of the green alga is > 1 ppm zinc, the Agency may consider waiving data for other algal species.



United States  
Environmental Protection  
Agency

Prevention, Pesticides  
and Toxic Substances  
(7510P)

September 2009

# **Zinc, Zinc Salts and Zeolites Final Work Plan Registration Review September 2009**

**Docket Number: EPA-HQ-OPP-2009-0011**  
**Zinc, Zinc Salts and Zeolites Final Work Plan**  
**Registration Review Case 4099**

Approved by: Joan Harrigan Farrelly  
Joan Harrigan-Farrelly, Director  
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Date: 9/14/09

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## **I. Introduction:**

This is EPA's Final Work Plan for the registration review of zinc, zinc salts and zeolites. The work plan includes the expected registration review timeline. The work plan also addresses public comments received concerning the Preliminary Work Plan in the Summary Document which was posted in the zinc, zinc salts and zeolites registration review docket, and any other comments concerning the initial docket postings. The Summary Document provided information on what EPA knows about the pesticide and what additional risk analyses and data or information the Agency believes are needed to make a registration review decision.

The Agency has begun to implement the new Registration Review program pursuant to FIFRA Section 3(g) and intends to review each registered pesticide approximately every 15 years to determine whether it continues to meet the FIFRA standard for registration. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state clearly what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

The Zinc, Zinc Salts and Zeolites Preliminary Work Plan was published in the federal docket on March 25, 2009. An amendment that included updated water-body impairment information was published in the federal docket on March 31, 2009. The 90-day comment period ended on June 23<sup>rd</sup>, 2009. The Preliminary Work Plan document is available on [www.regulations.gov](http://www.regulations.gov), docket number EPA-HQ-OPP-2009-0011.

## **II. Summary of Comments Received on Preliminary Work Plan:**

EPA received one whitepaper containing several separate comments during the public comment period on the initial docket, described below. The data needs, work plan and timeline described in the Preliminary Work Plan remain as they were presented initially. This document makes final the work plan for the zinc, zinc salts and zeolites registration review process.

Comment: The Agency has sufficient information to fully evaluate the potential risks of exposure to zinc or silver zeolites and should revise its registration review work plan accordingly.

Response: As cited on page 7 and 8 of "Summary of Human Health Effects Data for Zinc, Zinc Salts and Zeolites Registration Review Document", dated March 4, 2009:

*The silver-zinc zeolites labels are unique from the rest of the zinc salt active ingredients because they are used for indirect food contact uses (countertops, appliances, kitchen hardware, tiles, food trays, food processing equipment, food storage containers, food packaging, food processing utensils). Because of the unique chemistry of the silver-zinc zeolites and the fact that these products are used for indirect food uses, additional silver-zinc toxicity data are needed for a dietary assessment.*

*According to EPA's review<sup>1</sup> "the registrant must submit or cite valid toxicology studies conducted with the end use formula silver-zinc product for sub-chronic toxicity in the rodent, sub-chronic toxicity in the non-rodent, developmental toxicity in the rodent, and reproductive toxicity in the rodent. Separate toxicity studies with technical grade silver and technical grade zinc are not required, but toxicity data on the formula with the highest percentage of silver and zinc should be conducted. This will support other end-use formulations from the registrant containing lower percentages of silver and zinc."*

*In reviewing silver and zinc containing compounds, AD decided that zeolites compounds may have their own toxicological pattern and zeolite-based silver-zinc active ingredients were not similar to salts of silver and hazards would need to be considered separately.<sup>2,3</sup>*

In summary, during registration of the silver-zinc zeolite products, the Agency had previously determined that the zeolites are unique chemically and toxicologically from the other silver and zinc products. The EPA concluded that chemically, zeolite-based silver active ingredients were not similar to salts of silver and zinc and hazards would need to be considered separately.

In registration review, EPA will examine the hazard databases for the silver-zinc zeolites and attempt to determine whether changes in science policy or deficiencies in the databases materially affected the overall risk picture. During the literature search the Agency identified the data gaps in the silver-zinc zeolite toxicology database based on the review of the existing Agency records. The data gaps are presented in Section III of this document.

The Agency could not conduct a dietary review because the proper toxicity information was not available as per an earlier Agency review. In addition to this review, other silver zeolite decision documents were referenced to provide context on the Agency's position on toxicity data requirements as far as Silver and Silver-Zinc Zeolites.<sup>2,3</sup>

**Comment: 90-day dermal toxicity in rodents** - It is possible to conclude that zeolites are not expected to result in systemic toxicity from the dermal route of exposure. Based on their poor water solubility and ionic characteristics, these compounds are not expected to cross the intact skin barrier and dermal uptake is negligible. Even in the case of damaged skin, uptake is expected to be negligible because of poor water solubility and their ionic nature (Fruijtier-Polloth (2009) HERA (2004)).

**Response:** The Agency will review the sources [(Fruijtier-Polloth (2009) and HERA (2004))] during the registration review process to determine whether a waiver is in order. To date, the Agency is not aware of a 90-day dermal toxicity study that has been submitted or identified in the existing literature for silver-zinc zeolites and can not draw any conclusions on whether dermal absorption is negligible.

**Comment: 90-day oral, developmental, reproductive studies** - Since the Agency failed to provide a clear explanation for its request for more data, publicly

available information on the reported effects from silver and/or silver/zinc zeolite-type products was reviewed to determine whether sufficiently different effects from those expected from either the active ingredient or the inert component could be identified.

The registrant referenced publicly available EPA reviews of data submitted to EPA, and noted that it is extremely difficult to clearly identify from the EPA reviews exactly what comprised the test material, even in terms of the metal components of the zeolite. If other components were present in the test material, the potential effects associated with those components cannot be identified. The registrant concluded from these publicly-available reviews that no sufficiently different effects were found, and no further toxicity data should be needed to complete Registration Review.

*Response:* The Agency has determined that there is a potential for dietary exposure in the registration review and provided context and references to support its position. The purpose of this registration review scoping document was to determine whether sufficient data are available to support registration review. Based on researching existing Agency reviews to date on the silver-zinc zeolites, this registration review concluded more toxicity data is needed for silver-zinc zeolites. This decision reflects previous Agency decisions and documents on file. The Agency has a limited toxicity database of existing literature and registrant submitted studies for silver-zinc zeolites and the Agency encourages submission of studies. The Agency has appreciated the feedback on the Preliminary Work Plan and the information provided by the registrant during the public comment period and anticipates further discussions at a later time. The EPA will review the public comment period submissions and will decide whether any of this data presented in the submission will affect the anticipated toxicity data needs.

According to registration records, the Agency had required toxicity data for silver-zinc zeolites in the past. In fact, the existing silver-zinc zeolite existing labels (EPA Reg 40810-12, 40810-24, etc.) express toxicity data needs and stipulate only time-limited approvals to support the indirect food uses. The registrant pointed out some toxicity information on inert zeolite, silver, zinc, silver copper zeolites, and silver zeolites in their response submissions. However, the registrant did not cite many specific toxicity studies of silver zinc zeolites and the Agency can not draw any meaningful comparisons or conclusion based on limited information. The Agency needs specific silver-zinc zeolite toxicity data to make meaningful conclusions on the differing toxicity of silver-zinc zeolites from other silver zeolites, and/or silver, and zinc ions, etc. to see if the toxicity is comparable or not. At this time the EPA has taken the position that toxicity of silver salts and silver zeolites are not comparable and in the review of Irgaguard B5000, the Agency were not able to resolve the existing toxicity data needs.<sup>2,3</sup> In the past for silver zeolites, the Agency has concluded that silver zeolite was not similar to salts of silver.<sup>2</sup> There is uncertainty on how the addition of different proportions of silver and zinc ions in different zeolite carriers would influence the dose related toxicity in different target organs.

*Comment:* Documentation has been submitted to FDA (as well as to EPA) that provides evidence that the IEC component of the Irgaguard products remain within the

preserved materials. These studies were conducted to support FDA Effective Food Contact Notifications (FCN#193, #248, #275, #294) for the Irgaguard products as components of polymers used in food packaging and other food contact surfaces as regulated by FDA under FFDCA Section 409. For each of the three Irgaguard products, Ciba conducted worst-case migration studies following FDA guidance to determine potential movement out of a preserved article into food that contacts the surface of the article. In accordance with FDA guidance, the Irgaguard product was incorporated into Low Density Polyethylene (LDPE), which is considered to be a worst-case scenario. The maximum use rate of the Irgaguard product was used (3% w/w of the polymer). Small plaques (1 x 4 inch) of the LDPE were then subjected to severe conditions to determine migration of components out of the LDPE into a food simulant. The severe conditions included large surface area to volume ratio, exposure to an extremely aggressive food simulating solvent (10% ethanol with 1% sodium chloride), exposure for up to 10 days at 40°C with a 2 hour preheat at 100°C. The 1% sodium chloride solution was added to the standard FDA solvent (10% ethanol) because use of the ethanol alone resulted in no detectable levels of any of the potential migrating compounds. Ciba conducted preliminary work with the standard FDA solvents (10% and 95% ethanol). There were no detectable levels of silver using either standard solvent. The addition of a 1% NaCl solution was found to increase the ionic strength of the extractants, resulting in low but detectable levels of silver. The sodium from the sodium chloride is preferentially exchanged with silver and zinc on the surface of the LDPE wafer and to ensure maximum solubility of the inorganic silver and zinc ions.

Response: The Agency currently has one silver-zinc migration study (MRID 46174701):

Viczkus, J. (2003) Migration Study From Low Density Polyethylene (LDPE) Into 10% Ethanol With 1% Sodium Chloride: Irgaguard B7000. Project Number: FDA2002N04, B7000. Unpublished study prepared by Ciba Speciality Chemicals Corp. 71 p.

This study will be reviewed for acceptability during registration review. Thank you for bringing this information to our attention. If there are more silver-zinc migration studies, we would encourage submission of these documents as well.

Comment: There is no evidence of developmental toxicity in studies conducted by Kanebo with a silver-zinc zeolite comparable to Irgaguard B5000 (MRID 41638502, 42245403, 42653201, 42845701).

Response: The Agency will be reviewing the studies submitted by Kanebo (41638502, 42245403, 42653201, 42845701) for acceptability with GLN 870.3700 during registration review.

## References

<sup>1</sup>Irgaguard B5000: Request for assessment of risk from proposed food contact uses of the active ingredient. Memorandum from T. McMahon, PhD to Dennis Edwards/Marshall Swindell/Tony Kish, U.S.EPA/AD. March 6, 2003.

<sup>2</sup>U.S. EPA 2004a. Memorandum from J. Chen, PhD. to Norm Cook. Subject: Interim Position for Toxicological End-points for Silver. P.C. Code: 309200.

<sup>3</sup>U.S. EPA 2004b. Memorandum for T. McMahon to T. Kish/M.Swindell. Silver - Report of the Antimicrobials Division Toxicity Endpoint Committee (ADTC). October 20, 2004.

In addition to addressing the comments above, EPA has also included amended water body impairment information in this Final Work Plan. Please see “Revised Zinc, Zinc Salts and Zeolites Summary Document: Registration Review Preliminary Work Plan Addendum”, dated March 31, 2009, for additional information.

In the Preliminary Work Plan, the Agency solicited comments on three specific topics: environmental justice, water body impairment, and trade irritants. No comments or information were received during the comment period concerning these issues.

### **III. Risk Assessment and Data Needs:**

A Reregistration Eligibility Decision (RED) was completed for elemental zinc in 1992. However, to complete registration review, additional data are needed to conduct the human health and ecological risk assessments.

#### ***Human Health Risk***

Note: Several existing registrations exist for silver-zinc and zinc zeolites which are composed of zinc (elemental) (PC Code 129015). Zeolites are clay-like materials that can be combined with various metal ions. According to MRID 458033-01, “the silver-zinc zeolites are silver-zinc ion-exchange products which are stabilized by an inert ion exchange carrier.” The silver-zinc zeolites labels are unique from the rest of the zinc salt active ingredients because they are used for indirect food contact uses (countertops, appliances, kitchen hardware, tiles, food trays, food processing equipment, food storage containers, food packaging, food processing utensils); drinking water contact uses (tubing, plumbing supplies and fixtures); dermal contact (apparel items and interior furnishings) and HVAC uses. The other zinc salts are not used for food contact products. There are currently no tolerances or exemptions for the requirement of a tolerance for any zinc salts in this registration review case. A tolerance or exemption from the requirement of tolerance may be needed for zinc portion of silver-zinc zeolites for these indirect food uses.

#### **Acute Toxicity**

##### ***Zinc Chloride***

Data from the existing RED indicates that zinc chloride has an acute toxicity category II for acute oral (rat). It is a corrosive for the skin and eyes (acute toxicity

category I). The acute inhalation study for zinc chloride is assigned as acute toxicity category III.

#### *Zinc Oxide*

Data from the existing RED indicates that zinc oxide has an acute toxicity category IV for acute oral (rat). It is not a skin irritant (acute toxicity category IV) and only a mild eye irritant (acute toxicity category III). The acute inhalation studies were waived for the technical active ingredient.

#### *Zinc Sulfate Monohydrate*

Data from the existing RED indicates that zinc sulfate monohydrate has an acute toxicity category III for acute oral (rat). It is a mild eye irritant (acute toxicity category III). The acute inhalation, dermal and skin sensitization studies were waived for the technical active ingredient.

#### *Zinc (Elemental)*

Data for zinc (elemental) was not available from the existing RED. However, data from a product toxicity review containing 1.36% zinc indicates that zinc (elemental) has an acute toxicity category IV for acute oral, acute dermal and acute inhalation. It is a mild skin irritant (acute toxicity category IV) and mild eye irritant (acute toxicity category III) and a nonsensitizer.

#### Subchronic and Chronic Toxicity

The Food and Drug Administration (FDA) considers zinc chloride as generally recognized as safe (GRAS) for use in foods and nutrients under 21 CFR 182.8985 and 21 CFR 182.5991. The FDA also considers zinc oxide and zinc sulfate as GRAS for use in foods under 21 CFR 182.8991 and 182.8997, respectively. The FDA also considers zinc oxide and zinc sulfate as GRAS for use in nutrients under 21 CFR 182.5985 and 182.5997, respectively.

Zinc is ubiquitous in the environment and occurs in the earth's crust at an average concentration of approximately 70 mg/kg. This ion exists in the form of zinc salts such as zinc sulfide, zinc carbonate, and zinc oxide. Zinc is also an essential nutrient in the body. For toxicological concerns, there are adequate toxicology studies in the zinc database to evaluate incidental oral exposures. At high levels, oral exposure to zinc in animal studies may result in toxic effects such as pancreatic and renal lesions as well as histological alterations in the pituitary and adrenal glands. In general, the levels of zinc causing these toxicological effects occur at much higher dose levels than the level recommended for nutritional use and that is naturally available in food. Zinc is widely distributed in plants and animals, and is normally present in food. Zinc is also a normal part of metabolism in all living organisms. Based on this information, no toxicological endpoints were selected.

However, the silver-zinc zeolites labels are unique from the rest of the zinc and zinc salts active ingredients because they are used for indirect food contact uses (countertops, appliances, kitchen hardware, tiles, food trays, food processing equipment, food storage containers, food packaging, food processing utensils). Because of the unique chemistry of the silver-zinc zeolites and the fact that these products are used for indirect food uses, additional silver-zinc toxicity data are needed for a dietary assessment.

According to the Agency's review, "the registrant must submit or cite valid toxicology studies conducted with the end use formula silver-zinc product for subchronic toxicity in the rodent, subchronic toxicity in the non-rodent, developmental toxicity in the rodent, and reproductive toxicity in the rodent. Separate toxicity studies with technical grade silver and technical grade zinc are not required, but toxicity data on the formula with the highest percentage of silver and zinc should be conducted. This will support other end-use formulations from the registrant containing lower percentages of silver and zinc."

In reviewing silver and zinc containing compounds, the Agency has suggested that zeolites compounds may have their own toxicological pattern. Zeolite-based silver-zinc active ingredients are not similar to salts of silver and zinc, and hazards would need to be considered separately for each silver-zinc zeolite compound.

#### Dietary and Drinking Water Exposure

The Food and Drug Administration (FDA) considers zinc and zinc chloride as generally recognized as safe (GRAS) for use in foods and nutrients under 21 CFR 182.8985 and 21 CFR 182.5991. The FDA also considers zinc oxide and zinc sulfate as GRAS for use in foods under 21 CFR 182.8991 and 182.8997, respectively. Due to low toxicity concerns, EPA will not conduct a dietary risk assessment for zinc and zinc salts. EPA believes that zinc and zinc salts are not a concern at the current registered levels which are similar to those occurring naturally in food.

It should be noted, however, that there are several end-use silver-zinc zeolite registrations that have dietary and drinking water uses. The Agency will be reviewing silver and other related compounds (e.g. silver-zinc zeolites) on a case-by-case basis to determine whether the compound is similar to an existing class (e.g., silver salts, silver-zinc zeolites). For dietary exposure for silver-zinc compounds, the registrant must submit or cite valid toxicology studies conducted with the end-use silver-zinc product for subchronic toxicity in the rodent, subchronic toxicity in the non-rodent, developmental toxicity in the rodent, and reproductive toxicity in the rodent. Separate toxicity studies with technical grade silver and technical grade zinc are not required, but toxicity data on the formula with the highest percentage of silver and zinc should be conducted. This will support other end use formulations from the registrant containing lower percentages of silver and zinc. Once the Agency receives the appropriate toxicity data, the Agency will need to conduct a dietary assessment for silver-zinc zeolite.

### Occupational and Residential Exposure

For zinc and zinc salts there are currently 15 registered labels. Most of the uses include handler exposure to mixing/loading soluble concentrates and wettable powders during manufacturing of material preservatives and wood pressure treatment exposures to zinc from ammonical copper zinc arsenate (ACZA). There would also likely be dermal and inhalation exposure applying zinc preservative sprays to moss on walkways and roofs. Occupational postapplication exposure scenarios would include dermal and incidental ingestion from contact with wood products (utility poles, building poles, foundation piling, marine piling, etc.) and residential postapplication exposures would include dermal and incidental ingestion to treated countertops and treated apparel and pressure treated decks.

As mentioned in the toxicology section (section 2), zinc is ubiquitous in the environment and occurs in the earth's crust at an average concentration of approximately 70 mg/kg. Zinc is also an essential nutrient in the body and is GRAS in food as dietary supplements. At registered application rates, exposure to zinc salt pesticides is not likely to be higher than that which is found in ambient levels and at levels of zinc nutrient which are required by the human body.

For silver-zinc and zinc zeolites, the Agency may need to conduct occupational and/or residential exposure assessments, particularly from dermal contact, to treated apparel and incidental exposure via mouthing to treated fabrics.

### Aggregate and Cumulative Exposure

In examining aggregate exposure, EPA takes into account the available and reliable information concerning exposures to pesticide residues in food and drinking water, and non-occupational pesticide exposures. The Food and Drug Administration (FDA) considers zinc and salts as GRAS for use in foods. EPA believes zinc and salts are of low toxicity and EPA does not intend to develop aggregate exposure assessments for zinc and zinc salts to determine if certain use patterns pose any risk based on the calculated aggregate exposures. However, for silver-zinc zeolites, an aggregate assessment may be needed. At this time, EPA has not yet determined whether zinc and salts have a common mechanism with other compounds; consequently, a cumulative assessment will not be performed for either of these chemicals.

### ***Anticipated Human Health Data Needs***

In reviewing silver- and zinc-containing compounds, AD determined that zeolite compounds may have their own toxicological pattern and zeolite-based silver-zinc active ingredients were not similar to salts of silver and zinc and hazards would need to be considered separately for each silver-zinc zeolite compound. Therefore, for the purposes of registration review, toxicity data needs for the silver-zinc and zinc zeolites are as follows:

Human Health Toxicity Data Needs:

- (GLN 870.3100) 90-Day Oral Toxicity-rodent
- (GLN 870.3150) 90-Day Oral Toxicity-non-rodent
- (GLN 870.3250) 90-Day Dermal Toxicity-rodent
- (GLN 870.3700) Developmental Toxicity- rodent
- (GLN 870.3800) Reproductive Toxicity- rodent

Once the Agency receives and reviews these toxicological studies, additional occupational, dietary and aggregate assessments may be needed. Further information is available in “Summary of Human Health Effects Data for the Zinc, Zinc Salts and Zeolites Registration Review Decision Document” dated March 4, 2009.

***Anticipated Physical/ Chemical Property Data Needs***

All product chemistry data requirements have been fulfilled for zinc, zinc salts and zeolites. Therefore, no additional physical/chemical property data are needed. Further information is available in “Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for the Zinc Salts Registration Review Summary Document”, dated March 31, 2009.

***Ecological Risk***

The metal zinc has been identified as a cause of impairment for water bodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at [http://iaspub.epa.gov/tmdl\\_waters10/attains\\_nation\\_cy.cause\\_detail\\_303d?p\\_cause\\_group\\_id=706](http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=706). This list indicates 437 impairments listed for zinc in water and 10 for zinc in sediment. The Agency will determine whether pesticide use was a contributor and/or determine if use might occur in these watersheds.

Environmental fate and ecological risk assessments have not been conducted for the active ingredients in this case. The Agency anticipates conducting environmental fate and ecological risk assessments for outdoor residential uses for control of moss on roofs, decks, steps, patios, walks, bricks, cement, sidewalks, fences, fence posts, foundations and other outdoor structures made of composition shingles, wood, gravel, brick and unpainted cement.

Since most of the applied zinc salts will transform to zinc oxide/hydroxide, the ecological effects and environmental fate data requirements for zinc oxide are sufficient for the other active ingredients. For zinc chloride, the Agency anticipates needing some or all of, the ecological effects and environmental fate data requirements listed for zinc oxide in order to conduct the environmental fate and ecological risk assessments, including an endangered species assessment.

The Agency has not conducted a risk assessment that supports a complete endangered species determination. The ecological risk assessment planned during

registration review will allow the Agency to determine whether zinc, zinc salts and zeolites' use has "no effect" or "may affect" federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide's use "may affect" a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Service (the Services), as appropriate.

### ***Anticipated Environmental Fate and Ecological Data Needs***

The Agency anticipates needing the following data in order to conduct a complete environmental fate and ecotoxicity assessment, including an endangered species assessment for all uses:

#### Environmental Fate Risk Assessment Data Needs:

- (GLN 850.6800) modified activated sludge respiration inhibition; and
- (GLN 835.1110) activated sludge sorption isotherm

#### Ecological Risk Assessment Data Needs:

- (GLNs 850.4400 & 850.5400) algal toxicity (Tier II) using freshwater green alga, *Selenastrum capricornutum*.

### **Potential Zinc Oxide Ecological Effects and Environmental Fate Data for Outdoor Wood Preservative Uses**

If zinc oxide is intended for treatment of wood products used in outdoor scenarios (e.g., decks, decking materials, aquatic uses), the Agency anticipates needing some, or all of, the following data in order to conduct the environmental fate and ecological risk assessments, including an endangered species assessment. However, note that which data are required will depend on: the quantities of zinc oxide (and/or major degradates or metabolites) leaching from wood; the types of chemical(s) leaching from wood (e.g., parent compound, major degradates or metabolites); the outdoor use scenarios in which zinc oxide-treated wood may be used; and the Agency's evaluation of the leaching data along with the available use, effects, and exposure information for zinc oxide:

#### **Ecological Effects Studies:**

To support registration of wood preservatives, the following ecological effects and environmental data are required.

#### **a. Required (R) Ecological Effects Data:**

<u>Guideline Number</u>	<u>Description of Data Requirement</u>
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850.1010:	Aquatic invertebrate acute EC <sub>50</sub> using <i>Daphnia magna</i> (using TGAI and TEP) (satisfied);
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- 850.1075: Fish acute LC<sub>50</sub>s with a coldwater (rainbow trout, preferred) and a warmwater (bluegill sunfish, preferred) species (using TGAI and Typical End-Use Product (TEP) (satisfied);
- 850.2100: Avian acute oral LD<sub>50</sub> with bobwhite quail (preferred) or mallard duck (using Technical Grade Active Ingredient (TGAI) (satisfied);
- 850.4225: Seedling emergence - dose response using rice (*Oryza sativa*);
- 850.4250: Vegetative vigor - dose response using rice (*Oryza sativa*);
- 850.4400: Aquatic plant growth using floating macrophyte *Lemna gibba*; and
- 850.5400: Aquatic plant growth (algal and aquatic plant toxicity) - Tier II (dose response) (using TGAI or TEP) – Four species: freshwater green alga, *Selenastrum capricornutum*, blue-green cyanobacterium, *Anabaena flos-aquae*, the freshwater diatom, *Navicula pelliculosa*, and marine diatom, *Skeletonema costatum*.

**b. Conditionally-Required (CR) Ecological Effects Data:**

- 850.1025: Oyster acute (shell deposition) or
- 850.1055: Acute oyster embryo larval
  
- 850.1035: Acute Mysid
- 850.1045: Acute Penaeid
  
- 850.1075: Acute Fish Toxicity (estuarine/marine species) Acute LC<sub>50</sub>s/EC<sub>50</sub>s using estuarine/marine organisms (fish) species (using TGAI and TEP);
- 850.1300: Aquatic Invertebrate life cycle study (using most sensitive species - freshwater or estuarine/marine) Daphnid chronic toxicity test;
- 850.1350: Aquatic Invertebrate life cycle study (using most sensitive species - freshwater or estuarine/marine) Mysid chronic toxicity test;
- 850.1400: Fish early-life stage toxicity studies (using TGAI and most sensitive species - freshwater or estuarine/marine);
- 850.1500: Fish (freshwater and/or estuarine/marine species) life cycle study (using TGAI);
  
- 850.1710: Oyster BCF
- 850.1730: Fish BCF
- 850.1850: Aquatic organism bioavailability/biomagnifications, toxicity tests (using TGAI or PAIRA);
  
- 850.1735: Whole sediment, acute invertebrates (freshwater) (using TGAI);
- 850.1740: Whole sediment; acute invertebrates (estuarine/marine) (using TGAI);
- 850.1950: Field testing for aquatic organisms (estuarine/marine) (using TEP);
- 850.2200: Avian dietary LC<sub>50</sub> with bobwhite quail and/or mallard duck (using TGAI) (satisfied);
- 850.2300: Avian reproductive studies with bobwhite quail and/or mallard duck (using TGAI); and

- None: Whole sediment - chronic invertebrates (freshwater and/or estuarine/marine) (using TGAI or TEP).  
850.3020: Honeybee acute contact LD<sub>50</sub> (using TGAI);  
850.3030: Toxicity of residues to honeybees, "Honey Bee Toxicity of Residues on Foliage" (using TGAI);  
850.4300: Terrestrial Plants Field Study (using TGAI);  
850.4450: Aquatic Plants Field Study (using TGAI)

**c. Required Environmental Fate Data:**

<u>Guideline Number</u>	<u>Description of Data Requirement</u>
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- |           |  |
|-----------|--|
| 835.2240: | Photodegradation in water (using TGAI or PAIRA);   |
| 835.2240: | Photodegradation in soil (using TGAI or PAIRA);  |
| 835.1230/ | Leaching and/  |
| 835.1240: | Adsorption/Desorption studies (using TGAI or PAIRA);   |
| 835.4100: | Aerobic soil metabolism (using TGAI or PAIRA);   |
| None:     | Aquatic leaching from wood study. (For guidance refer to: Standard Method of Determining The Leachability of Wood Preservatives, American Wood-Preservers' Association Standard E11-06); |
| None:     | Soil leaching from wood study (AWPA E20-04)  |
| 835.4400: | Anaerobic aquatic metabolism (using TGAI or PAIRA); and  |
| 850.6800: | Modified activated sludge, respiration inhibition (using TGAI).  |

**d. Conditionally-Required (CR) Environmental Fate Data:**

- 835.4200: Anaerobic soil metabolism (using TGAI or PAIRA);  
835.4300: Aerobic aquatic metabolism (using TGAI or PAIRA);  
835.4400: Anaerobic aquatic metabolism (using TGAI or PAIRA);  
835.6200: Aquatic (sediment) [using Typical End-use Product (TEP)]; and  
None: Monitoring of representative U. S. waters (residue of concern).

The above listed data requirements for zinc oxide will also satisfy data requirements for residential outdoor moss control uses of zinc chloride, zinc sulfate monohydrate, and zinc metal.

**IV. Timeline:**

EPA has created the following estimated timeline for the completion of the zinc, zinc salts and zeolites registration review.

<b>Registration Review for Zinc, Zinc Salts and Zeolites Projected Registration Review Timeline</b>	
<b>Activities</b>	<b>Time</b>
Opening Docket	
Open Docket	Completed March 2009
Close Public Comment Period	Completed June 2009
Case Development	
Final Work Plan	September 2009
Issue DCI	June 2010
Data Submission	June 2011
Preliminary Risk Assessment	June 2013
Close Public Comment Period	September 2013
Registration Review Decision	
Proposed Registration Review Decision	December 2013
Public Comment Period	March 2013
Final Registration Review Decision & Begin Post-Decision Follow-up	2013
Total (years)	4

**Next Steps:**

A Data Call-In (DCI) will be developed regarding the data gaps listed under the “Risk Assessment and Data Needs” section. Also, human health and ecological assessments will be conducted for all uses.

**V. GLOSSARY of TERMS & ABBREVIATIONS**

ai	Active Ingredient
AR	Anticipated Residue
ASTM	American Society for Testing and Materials
AWPA	American Wood Preserver's Association
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC <sub>50</sub>	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD <sub>50</sub>	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAIRA	Pure Active Ingredient Radiolabelled
PCA	Percent Crop Area

PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q <sub>1</sub> *	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24(c) of FIFRA)
TGAI	Technical Grade Active Ingredient
TEP	Typical End-Use Product
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard